synapses (Finnerty et al., 1999), as well as the phenotype of subpopulations of interneurons (Carder et al., 1996). Indeed, recent work demonstrates that local inhibitory circuits drive competitive plasticity in the neocortex (Hensch et al., 1998). In the visual system, a lasting shrinkage of open eye representation can be obtained if intracortical inhibition is saturated during a period of monocular deprivation (Hata and Stryker, 1994). Could it be that the balance of excitation to inhibition in barrel cortex is tipped in favor of the latter during the brief exploratory bouts in a novel environment? The only way to find out will be to record chronically across multiple units and cortical layers during the actual behavior and plasticity process.

Finally, how such a shift in excitatory–inhibitory balance might be achieved is of interest. The brevity of the exploratory behavior required for bidirectional map changes is suggestive. Remarkably, just 4 min/week (of which only a fraction is spent actively scanning) in a novel environment over a month of deprivation is sufficient to shrink the spared whisker representation. Focal attention to a stimulus can enhance a cell's peak response (Gilbert, 1998) and has most often been linked with state-dependent activity of neuromodulatory systems (Weinberger, 1995). Increases in behaviorally relevant inputs require cholinergic input from the basal forebrain, whose stimulation can also modify cortical maps (Kilgard and Merzenich, 1998). It is tempting to speculate that the decreases reported by Polley et al. (1999) may be similarly regulated by diffuse systems that selectively modulate subsets of inhibitory interneurons (Kawaguchi and Shindou, 1998; Xiang et al., 1998). Would it be possible to replace the very brief behavioral exploration of a single whisker with exogenous neuromodulators to produce similar map changes in nondeprived animals?

Is there an advantage to shrinking cortical representations in the face of rich experience or is this just a by-product of competitive mechanisms? Perhaps a smaller, tighter representation is more efficient than a widely distributed one in certain cases. For example, in human mapping studies it has been observed that the dominant language occupies *less* territory than others in multilingual subjects (Ojemann, 1991). The results of Polley et al. (1999) offer an opportunity to understand how and under what behavioral conditions a particular direction for sensory map plasticity is favored.

Takao K. Hensch
Laboratory for Neuronal Circuit Development
Brain Science Institute
RIKEN
2–1 Hirosawa, Wako-shi
Saitama 351-0198
Japan

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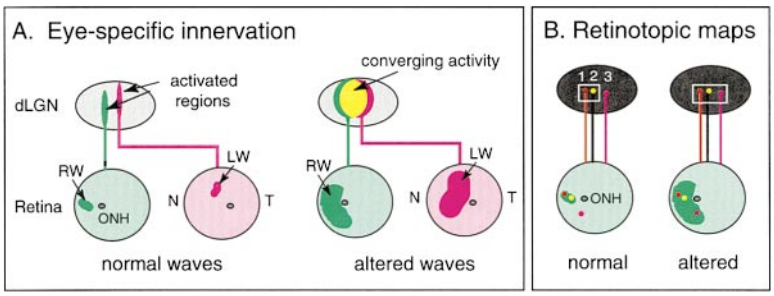
Retinal Waves: Stirring Up a Storm

In many parts of the developing nervous system, neuronal connectivity becomes more precise as some inputs are eliminated while others are maintained. This process of synaptic refinement requires neurotransmission (Lichtman et al., 1998). The temporal properties of this activity, rather than its mere presence, are thought to be necessary to drive segregation of competing inputs. In particular, much modeling work built on the initial theory by Hebb suggests that synchronous inputs are costrengthened, whereas asynchronous firing of inputs results in weakening of one set of connections (see, e.g., Miller, 1996). This theory is supported by experimental findings in which coactivated inputs are potentiated, whereas inputs are depressed when they are silent during postsynaptic activity (Lichtman et al., 1998). Although the actual withdrawal of synaptic contact due to asynchronous firing has not yet been observed experimentally, this simple theory has provided much impetus for a search for endogenous patterned activity during the period of synaptic refinement in the developing nervous system.

Patterned spontaneous activity has now been observed in many developing circuits, including neurons in the spinal cord, hippocampus, auditory nuclei, and retina (reviewed by O'Donovan, 1999; Wong, 1999). Neurons in all of these systems spontaneously fire rhythmic bursts of action potentials that are temporally synchronized between neighboring cells. The prevalence of this activity pattern in developing networks has long prompted the question of what competitive events might be driven by this activity. This question has been addressed extensively in the visual system.

Synchronized spontaneous retinal activity takes the form of propagating waves with the degree of coincident firing between cells decreasing as a function of intercellular distance. Waves are generated prior to vision (but disappear upon photoreceptor maturation) and are thought to bear spatiotemporal cues that guide the refinement of retinal ganglion cell projections to visual targets in the brain. In particular, it has been suggested that waves underlie the activity-dependent segregation of eye input and the refinement of retinotopic maps at subcortical visual targets, such as the dorsal lateral geniculate nucleus (dLGN) (Wong, 1999).

While retinal activity is needed for the emergence of



Effect of Wave Dynamics on the Degree of Coactivation of Neurons in the dLGN

(A) Normally, the probability of coincident firing between the left and right eyes is minimal because the waves occur relatively infrequently and cover a small region of retina within a fixed time window. This would favor segregation of left and right eye inputs at the dorsal lateral geniculate nucleus (dLGN). Waves traveling faster and more frequently and covering a greater area would increase the probability of synchronous firing between inputs converging onto the same dLGN neurons (yellow area). Abbreviations: T, temporal; N, nasal retina; RW, right eye wave; LW, left eye wave.

(B) Visual space is systematically represented in the dLGN; refinement of the retinotopic map could occur based on the propagation of waves. Normally, neighboring cells 1 and 2 are more coincident (box) in their firing and uncorrelated with the activity of a more distant cell 3. If waves are significantly larger, the firing of all three cells will be better synchronized, thus potentially decreasing the precision of map refinement. Abbreviation: ONH, optic nerve head.

normal eye-specific layers in the dLGN (Penn et al., 1998), it is still unclear whether activity in the form of waves is necessary. Blocking activity also suppresses map refinement, but as yet there is no direct demonstration that waves are necessary for sharpening retinotopic projections, although theory suggests that waves contain appropriate temporal cues for map refinement (Wong, 1999). To address these issues, it is necessary to perturb the waves without abolishing activity altogether. The primary objective would be to alter the degree of synchronous firing either between the two eyes or within one eye. The degree of synchronous firing depends on the width and frequency of the waves and the speed of the wavefront (see Feller et al., 1997). The width and speed define the area of retina and therefore (approximately) the number of neighboring retinal ganglion cells that fire together within a particular time window. The frequency of the waves determines how often a particular region of retina is activated per unit time. Thus, qualitatively, for a given time interval, one would expect that significant changes in one or all of these parameters would alter the probability of coincident firing between the two eyes or between cells within one eye.

Perturbation of wave dynamics could be achieved in at least two ways. The first is to stimulate the optic nerves in vivo (Weliky and Katz, 1997). Firing between eyes and within an eye can then be regulated artificially. Another way is to chronically perturb waves by intraocular injections of pharmacological agents. In order to do so, we require knowledge of the cellular mechanisms controlling the spatial and temporal properties of the waves. It is now known that during early development, correlated bursting activity depends on cholinergic transmission (Feller et al., 1996; Sernagor and Grzywacz, 1996, 1999). Cholinergic starburst cells in the retina also contain the neurotransmitter γ-aminobutyric acid (GABA) and the neuromodulator adenosine. In a paper by Stellwagen et al. (1999 [this issue of *Neuron*]), the authors have painstakingly dissected the contributions of acetylcholine, GABA, and adenosine in regulating wave dynamics. They found that endogenous adenosine, acting via the cAMP–PKA pathway, regulates the width, speed, and frequency of the waves. When cAMP is raised above normal, waves cover a much larger area of retina, travel faster, and occur more frequently. When cAMP is lowered below normal, the waves are smaller, slower, and less frequent. Thus, wave dynamics could be regulated by the levels of adenosine, although how adenosine acts in this fashion has yet to be elucidated. The "mega-waves" that are observed when cAMP levels are high would lead to a higher probability of coincident firing between eyes, and would certainly increase correlated firing between distant cells within an eye (see figure).

The findings of Stellwagen et al. (1999) now offer new opportunities for us to directly assess the developmental function of waves in vivo. It will be most interesting to compare the effects of increasing or decreasing the various parameters of the waves on the development of retinogeniculate connectivity. In order to fully understand the outcome of such future manipulations, however, two additional pieces of information will be useful. The first concerns knowledge of how the waves assessed by calcium imaging correspond to the spike distributions of neighboring retinal ganglion cells, both in the normal and in the altered conditions. Interestingly, in elevated cAMP, not only do waves occur more frequently, but calcium "peaks" ride above an elevated baseline—whether this increased baseline constitutes additional information in the spike trains would be interesting to assess. Second, to understand how synchronous or asynchronous firing might regulate the process of eye-specific segregation or the refinement of retinotopic maps, we need to determine how postsynaptic dLGN neurons use spike information carried by waves to drive these developmental events (Miller, 1996).

Finally, the authors raise the possibility that spontaneous retinal activity via adenosine signaling is also involved in maturation events of the retina. Already there is growing support for a role of spontaneous activity in retinal development. Early neurotransmission regulates the dynamic remodeling of retinal ganglion cell dendrites during synaptogenesis (Wong and Wong, 2000) and influences the maturation of their receptive fields (Sernagor and Grzywacz, 1996). Thus, spontaneous activity may not only help sculpt the axonal projections of retinal ganglion cells, but it may also contribute to shaping ganglion cell dendritic patterns and intraretinal connectivity.

Rachel O. L. Wong
Department of Anatomy and Neurobiology
Washington University School of Medicine
St. Louis, Missouri 63130

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Calcium on the Up: Supralinear Calcium Signaling in Central Neurons

The pioneering experiments of the remarkable Russian behaviorist Ivan Pavlov firmly seeded the idea that associative interactions are a crucial element in the formation of new memories. The precise neural basis for Pavlov's observations are still, to this day, a matter of conjecture, but there is a keen recognition that the neural substrate of memory formation must involve some form of coincidence detection. That the NMDA receptor, which requires both glutamate binding and membrane depolarization to allow calcium influx, is capable of coincidence detection is not in doubt. Recently, however, a number of studies have raised the possibility that other elements of a neuron's intracellular machinery may also provide a mechanism for coincidence detection.

The first hint of a new coincidence detection mechanism in neurons came from Yuste and Denk (1995), in a paper that introduced the use of two-photon microscopy as a method for imaging calcium transients in dendritic spines of hippocampal pyramidal cells. Yuste and Denk were able to image a rise in intracellular calcium within spines in response to synaptic stimulation but, intriguingly, found that the pairing of an action potential with synaptic stimulation resulted in a supralinear calcium accumulation within the spine. In this context, supralinearity is defined as a calcium transient with a magnitude greater than the sum of its component parts; that is to say, it is larger than the computed sum of the calcium influx arising from both the action potential and synaptic activation. The functional importance of this observation became apparent from papers published subsequently by Markram et al. (1997) and Magee and Johnson (1997). Each showed that the pairing of a backpropagating action potential with synaptic activation resulted in the generation of robust long-term potentiation (LTP). Furthermore, Magee and Johnson explicitly demonstrated that this LTP-inducing protocol produced a supralinear calcium signal. The full physiological significance of a supralinear calcium signal has not, however, been definitively established. This would require one to show that a block of the supralinear component of the calcium response also blocked the induction of LTP.

Given the possibility that supralinear calcium signals are physiologically significant, it becomes important to understand their mechanistic basis. One possibility is that the backpropagating action potential transiently removes the magnesium block of the NMDA receptors, thereby augmenting the calcium signal (Koester and Sakmann, 1998). Whether such a mechanism would adequately explain the supralinearity of the calcium signal is, however, hard to judge in the absence of data detailing the extent to which either the synaptic input or an action potential depolarizes the spine head. A second possibility was suggested by Schiller et al. (1998) on the basis of experiments in which they photolysed caged glutamate to produce a controlled level of postsynaptic activation, while simultaneously imaging the resulting calcium transient in dendritic spines. This approach reduces the concern that pharmacological manipulations may also impact on the presynaptic neuron and allowed Schiller et al. (1998) to explore explicitly the role played by voltage-sensitive calcium channels. The experiments reveal that nonlinear activation of voltage-sensitive calcium channels augments the synaptic signal when paired with an action potential and that the level of augmentation is adequate to explain the calcium supralinearity. This approach does, however, have some limitations. For example, the authors take great care to produce an electrical response following photolysis that mirrors a synaptically evoked excitatory postsynaptic potential (EPSP); however, in reality synaptically evoked responses are likely to arise from the sum of several afferent inputs that are distributed at many sites across the postsynaptic cell. By contrast, photolysis yields an EPSP that arises within the restricted volume of the photolysed compound; such restricted release may well produce a local depolarization that is considerably greater than that produced by any single synaptic event.

There is, however, a third way in which supralinear calcium signals might be achieved. This involves the release of calcium from intracellular stores. The release of calcium from intracellular stores of central neurons was first shown by Alford et al. (1993). Korkotian and Segal (1998) subsequently demonstrated that dendritic spines contained functional calcium stores, and Emptage et al. (1999) showed that activation of these stores could be achieved by single synaptic stimuli. Nakamura et al. (1999 [this issue of *Neuron*]) specifically address the question of whether calcium release from stores, when paired with backpropagating action potentials, participates in the generation of supralinear calcium signals. To do so, they used a cooled CCD system to achieve high-speed fluorescent images of hippocampal pyramidal cells loaded with one of two calcium-sensitive dyes, bis-fura-2 or furaptra. They specifically concentrated their investigation on the contribution of the